

Claims

1. A pharmaceutical product suitable for administration of allergen comprising
a fast-dispersing, non-compressed solid dosage form suitable for oromucosal
5 administration including:
 - (a) a matrix formed from at least one matrix-forming agent, and
 - (b) an effective dose of an allergen for desensitizing an individual to said allergen,wherein
- 10 (c) the loss of the allergen content in said dosage form is less than 50% of the initial allergen content after being held for 3 months at 25°C and 60% relative humidity, and
- (d) the loss of allergen content from said solid dosage form is less than about 0.5 µg allergen extract or less than about 0.05 µg major allergen
15 when subjected to a friability test.
2. A pharmaceutical product according to claim 1, wherein the friability is measured in a friability test as described in European Pharmacopoeia 2.9.7.
3. A pharmaceutical product according to claim 1 wherein the friability is measured in a friability test comprising the following steps
20 (a) placing individual sealed blisters each containing a solid dosage form in equipment suitable for friability measurements;

- (b) moving the sealed blister containing the solid dosage form for an appropriate time and at an appropriate velocity;
 - (c) removing the sealed blister containing the solid dosage form ;
 - (d) opening the blister and placing the solid dosage form and any
5 residues in a container;
 - (e) removing the solid dosage form from the container leaving any loose residuals in said container;
 - (f) performing an allergen specific assay on said residues determining the allergen content in said residues; and optionally calculating the
10 percentage allergen content in said residues of the total allergen content of the solid dosage form unit.
4. A pharmaceutical product according to claim 3, wherein
- (a) between 1 and 100 blisters containing the solid dosage form are used,
 - (b) an equipment for friability measurements as described in European
15 Pharmacopoeia 2.9.7 is used
 - (c) the solid dosage forms are rotated for 100 turns at 25 ± 1 rpm, and
 - (d) the allergen specific assay is an immunochemical allergen specific assay.
5. A pharmaceutical product according to claim 3, wherein the allergen
20 specific assay is an enzyme-linked immunosorbant assay.
6. A pharmaceutical product according to claim 1 containing from about 2.5 μg to about 3.75 mg allergen extract.
7. A pharmaceutical product according to claim 6 containing from about 2.5 μg to about 2.5 mg allergen extract.

8. A pharmaceutical product according to claim 7 containing from about 25 μg to about 2.5 mg allergen extract.
9. A pharmaceutical product according to claim 8 containing from about 25 μg to about 1.25 mg allergen extract.
- 5 10. A pharmaceutical product according to claim 9 containing from about 25 μg to about 1 mg allergen extract.
11. A pharmaceutical product according to claim 10 containing from about 25 μg to about 750 μg allergen extract.
12. A pharmaceutical product according to claim 1 containing from about 0.25 μg to about 0.25 mg major allergen.
- 10 13. A pharmaceutical product according to claim 12 containing from about 2.5 μg to about 0.25 mg major allergen.
14. A pharmaceutical product according to claim 13 containing from about 2.5 μg to about 0.125 mg major allergen.
- 15 15. A pharmaceutical product according to claim 14 containing from about 2.5 μg to about 0.1 mg major allergen.
16. A pharmaceutical product according to claim 15 containing from about 2.5 μg to about 75 μg major allergen.
17. A pharmaceutical product according to claim 1 containing a dose from about 65 to about 15,000 BAU.
- 20

18. A pharmaceutical product according to claim 17 containing a dose of about 650 to about 15,000 BAU.
19. A pharmaceutical product according to claim 18 containing a dose of about 650 to about 6,000 BAU.
- 5 20. A pharmaceutical product according to claim 19 containing a dose of about 650 to about 4,700 BAU.
21. A pharmaceutical product according to claim 20 containing a dose of about 650 to about 3,500 BAU.
22. A pharmaceutical product according to claim 17, wherein the allergen is a
10 grass pollen allergen.
23. A pharmaceutical product according to claim 1, wherein the allergen content loss is less than about 30 % of the initial content after being held for 3 months at 25°C and 60% relative humidity.
24. A pharmaceutical product according to claim 23, wherein the allergen
15 content loss is less than about 20 % of the initial content after being held for 3 months at 25°C and 60% relative humidity.
25. A pharmaceutical product according to claim 24, wherein the allergen content loss is less than about 15 % of the initial content after being held for 3 months at 25°C and 60% relative humidity.
- 20 26. A pharmaceutical product according to claim 25, wherein the allergen content loss is less than about 10% of the initial content after being held for 3 months at 25°C and 60% relative humidity.

27. A pharmaceutical product according to claim 26, wherein the allergen content loss is less than about 5% of the initial content after being held for 3 months at 25°C and 60% relative humidity.
28. A pharmaceutical product according to claim 27, wherein the allergen
5 content loss is less than about 2% of the initial content after being held for 3 months at 25°C and 60% relative humidity.
29. A pharmaceutical product according to claim 1, wherein the loss from each solid dosage form is less than about 0.25 µg allergen extract
30. A pharmaceutical product according to claim 29, wherein the loss from
10 each solid dosage form is less than about 0.15 µg allergen extract.
31. A pharmaceutical product according to claim 30, wherein the loss from each solid dosage form is less than about 0.075 µg allergen extract.
32. A pharmaceutical product according to claim 31, wherein the loss from each solid dosage form is less than about 0.025 µg allergen extract.
- 15 33. A pharmaceutical product according to claim 32, wherein the loss from each solid dosage form is less than about 0.01 µg allergen extract.
34. A pharmaceutical product according to claim 1, wherein the loss from each solid dosage form is less than about 0.025 µg major allergen.
35. A pharmaceutical product according to claim 34, wherein the loss from
20 each solid dosage form is less than about 0.015 µg major allergen.
36. A pharmaceutical product according to claim 35, wherein the loss from each solid dosage form is less than about 0.0075 µg major allergen.

37. A pharmaceutical product according to claim 36, wherein the loss from each solid dosage form is less than about 0.0025 µg major allergen.
38. A pharmaceutical product according to claim 37, wherein the loss from each solid dosage form is less than about 0.001 µg major allergen.
- 5 39. A pharmaceutical product according to claim 1, wherein the matrix is formed by subliming a solution comprising said allergen and at least one matrix-forming agent.
40. A pharmaceutical product according to claim 1, wherein the water content of the dosage form is between about 2 % and about 8% by weight.
- 10 41. A pharmaceutical product according to claim 40, wherein the water content of the dosage form is between about 4 % and about 7 % by weight.
42. A pharmaceutical product according to claim 1, wherein one matrix-forming agent is gelatine.
43. A pharmaceutical product according to claim 42, wherein the gelatine
15 comprises fish gelatine.
44. A pharmaceutical product according to claim 43, wherein a further matrix-forming agent is mannitol.
45. A pharmaceutical product according to claim 44, wherein the ratio of fish gelatine to mannitol is from about 2:20 to about 20:1.
- 20 46. A pharmaceutical product according to claim 45, wherein the ratio of fish gelatine to mannitol is from about 2:10 to about 10:1.

47. A pharmaceutical product according to claim 46, wherein the ratio of fish gelatine to mannitol is from about 3:5.5 to about 6.5:3.
48. A pharmaceutical product according to claim 47, wherein the ratio of fish gelatine to mannitol is 4:3.
- 5 49. A pharmaceutical product according to claim 47, wherein the ratio of fish gelatine to mannitol is s 6.5:5.5.
50. A pharmaceutical product according to claim 47, wherein the ratio of fish gelatine to mannitol is 6.0:5.08.
51. A pharmaceutical product according to claim 44, wherein the matrix is
10 formed from a solution comprising about 2 to about 10% W/W fish gelatine and about 1 to about 10% mannitol W/W.
52. A pharmaceutical product according to claim 51, wherein the solution comprises about 3 to about 6.5% W/W fish gelatine and about 3 to about 5.5 % W/W mannitol.
- 15 53. A pharmaceutical product according to claim 52, wherein the solution comprises about 6.5 % W/W fish gelatine and about 5.5 % W/W mannitol.
54. A pharmaceutical product according to claim 52, wherein the solution comprises 6.0 % W/W fish gelatine and 5.08 % W/W mannitol.
55. A pharmaceutical product according to claim 1, wherein one matrix-
20 forming agent is starch.
56. A pharmaceutical product according to claim 55, wherein a further matrix-forming agent is mannitol.

57. A pharmaceutical product according to claim 56, wherein the ratio of starch to mannitol is from about 2:20 to about 20:1.
58. A pharmaceutical product according to claim 56, wherein the ratio of starch to mannitol is from about 2:10 to about 10:1.
- 5 59. A pharmaceutical product according to claim 56, wherein the matrix is formed from a solution comprising 3-6.5% W/W starch and 3-5.5% W/W mannitol.
60. A pharmaceutical product according to claim 1, which disintegrates in human saliva within about 60 seconds.
- 10 61. A pharmaceutical product according to claim 60, which disintegrates in human saliva within about 30 seconds.
62. A pharmaceutical product according to claim 61 which disintegrates in human saliva within about 10 seconds.
63. A pharmaceutical product according to claim 62, which disintegrates in
15 human saliva within about 5 seconds.
64. A pharmaceutical product according to claim 63, which disintegrates in human saliva within about 2 seconds.
65. A pharmaceutical product according to claim 1, wherein the allergen is selected from the group consisting of tree pollen allergens, grass pollen
20 allergens, mite allergens, insect allergens, venom allergens, animal hair allergens, dander allergens and food allergens.

66. A pharmaceutical product according to claim 65, wherein the allergen is in the form of an extract, a purified allergen, a modified allergen or a recombinant allergen or a mutant of a recombinant allergen or any combination thereof.
- 5 67. A pharmaceutical product according to claim 65, wherein the allergen is grass pollen allergen.
68. A pharmaceutical product according to claim 67, wherein the allergen is in the form of grass extract.
69. A pharmaceutical product according to claim 65, wherein the allergen is
10 dust mite allergen.
70. A pharmaceutical product according to claim 69, wherein the allergen is in the form of a dust mite extract.
71. A pharmaceutical product according to claim 1 comprising at least two different allergens.
- 15 72. A pharmaceutical product according to claim 1, wherein the variation in allergen content of allergen between different solid dosage forms is within about 10%.
73. A pharmaceutical product according to claim 72, wherein the variation in content of allergen between different solid dosage forms is within about 7%.
- 20 74. A pharmaceutical product according to claim 73, wherein the variation in content of allergen between different solid dosage forms is within about 5%.

75. A pharmaceutical product according to claim 1, wherein the solid dosage form has a tensile strength of less than about 1.0 N/mm².
76. A pharmaceutical product according to claim 1, wherein said solid dosage form has a Peak load to Fracture of not less than about 0.05 KgF and below
5 about 0.9 KgF.
77. A pharmaceutical product according to claim 1, wherein said dosage form is sufficiently strong to be removed from a blister pack without releasing residues containing more than about 0.5 µg extract to the surroundings.
78. A pharmaceutical product according to claim 1, wherein said dosage form
10 is sufficiently strong to be removed from a blister pack without releasing residues containing more than about 0.05 µg major allergen to the surroundings.
79. A pharmaceutical product according to claim 1, wherein said dosage form is sufficiently strong to be removed from a blister pack without releasing residues containing more than about 13 BAU to the surroundings.
- 15 80. A pharmaceutical product according to claim 1 wherein the dosage form comprises one or more excipients.
81. A pharmaceutical product according to claim 80, containing an excipient selected from the group consisting of antacids, diluents, mucoadhesive agents, enhancer, flavouring agents, taste masking agents, preservatives, antioxidants,
20 surfactants, viscosity enhancers, coloring agents, pH modifiers and sweeteners.
82. A pharmaceutical product according to claim 1, further comprising an adjuvant.

83. The pharmaceutical product of claim 82, wherein the adjuvant is selected from the group consisting of aluminium salts, non-toxic bacterial fragments, cytokines, cholera toxin, detoxified fractions cholera toxin, chitosan, heat-labile fragments of E.coli, detoxified fractions heat-labile fragments of E.coli, saponins, lipopoly-saccharides, muramyl dipeptide, liposomes, Immune stimulatory DNA sequences and lactide/glycolide microparticulate polymers.
84. A pharmaceutical product according to claim 1, further comprising an anti-allergic drug.
85. A pharmaceutical product according to claim 84, wherein the anti-allergic drug is an antihistamine.
86. A multi dosage container comprising a plurality of solid dosage forms of claim 1.
87. A multi dosage container according to claim 86, wherein the multi dosage container is a blister pack.
88. A multi dosage container according to claim 86, wherein the multi dosage container is an all aluminium blister pack.
89. A multi dosage container according to claim 86, wherein the multi dosage container is a multilayered all aluminium blister pack.
90. A method of treating allergy or alleviating symptoms of allergy comprising oromucosal administration of the pharmaceutical product of claim 1.
91. A method of producing a fast-dispersing, non-compressed solid and stable dosage form having low friability, comprising at least one matrix forming

agent and being suitable for oromucosal administration comprising an effective dose for desensitizing an individual to at least one allergen, comprising the steps of

- 5 (a) preparing an aqueous solution comprising said at least one allergen and said at least one matrix forming agent,
- (b) introducing the solution into one or more depressions in a mould
- (c) subjecting the loaded mould to freezing and freeze-drying using standard conditions of shelf temperature and chamber pressure to obtain said solid dosage form in each depression.

10 92. A method according to claim 91 wherein step (b) comprises introducing the solution into depressions in a multilayer laminated blister sheet.

93. A method of measuring the friability of a solid dosage form as defined in claim 1 comprising the following steps;

- 15 (a) placing individual sealed blisters each containing a solid dosage form in equipment suitable for friability measurements;
- (b) moving the sealed blister containing the solid dosage form for an appropriate time and at an appropriate velocity;
- (c) removing the sealed blister containing the solid dosage form ;
- (d) opening the blister and placing the solid dosage form and any
20 residues in a container;
- (e) removing the solid dosage form from the container leaving any loose residuals in said container;
- (f) performing an allergen specific assay on said residues determining the allergen content in said residues; and optionally calculating the

percentage allergen content in said residues of the total allergen content of the solid dosage form unit.

94. A method according to claim 93 wherein
- 5 (a) between 1 and 100 blisters containing the solid dosage form are used,
(b) an equipment for friability measurements as described in European Pharmacopoeia V.2.9.7 is used,
(c) the solid dosage forms are rotated for 100 turns at 25 ± 1 rpm, and
(d) the allergen specific assay is an immunochemical allergen specific assay.
- 10 95. A method according to claim 94 wherein the immunochemical assay is an enzyme-linked immunosorbant assay.
96. The dosage form as defined in claim 1, wherein the solid dosage form has a water activity of 0.4-0.5.
97. A kit for treatment of allergy or for alleviating allergy symptoms
- 15 comprising
- a) a plurality of solid oral dosage forms in a sealed container, each of said solid oral dosage forms being held in a sealed enclosure and comprising an effective amount of an allergen suitable for oromucosal administration; and
- 20 b) each of said solid dosage forms containing the same amount of the allergen.
98. A kit according to claim 97 further comprising instructions for using the multiple solid dosage forms.

99. A kit according to claim 97, wherein the dosage form is a fast-dispersing dosage form.
100. A kit according to claim 97, wherein each of the solid dosage forms are located in individually sealed blisters in a multiple blister pack.
- 5 101. A kit according to claim 97, wherein the solid dosage forms comprise gelatine.
102. A kit according to claim 101, wherein the solid dosage forms further comprise mannitol.
103. A kit according to claim 101, wherein the gelatine is fish gelatine.
- 10 104. A kit according to claim 97, wherein the effective amount of allergen is between about 2.5 µg – about 3.75 mg extract /solid dosage form.
105. A method for treating a mammal patient afflicted with allergy, comprising:
- a) providing a kit according to claim 97, and
- b) repeatedly administering to said human at least one of said solid
- 15 dosage forms from the kit until the allergy symptoms are relieved, wherein the repeated administration lacks an updosing step.
106. A pharmaceutical product comprising an orally administerable solid dosage form comprising a matrix formed of at least one pharmaceutically acceptable material, an effective amount of an allergen for desensitizing a
- 20 human to said allergen, said dosage form having an allergen content at least about 50% of the initial allergen content after being held for 3 months at 25°C and 60% relative humidity.

107. A pharmaceutical product according to claim 1, wherein the product is selected from the group consisting of a lozenge, tablet, a capsule and a caplet.
108. A pharmaceutical product according to claim 1 for oromucosal treatment of allergy or alleviation of allergy symptoms.
- 5 109. A method of treating allergy or alleviating symptoms of allergy comprising oromucosal administration of the solid dosage of claim 1.